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Summary

Ecstatic auras are a rare but compelling epileptic entity. During the first seconds of the seizure, ecstatic auras provoke feelings of well-being, intense serenity, bliss, and enhanced self-awareness. They can be associated with the impression of dilated time, and are sometimes described as a mystic experience by some patients. The functional neuroanatomy of ecstatic seizures is still debated. During recent years several patients presenting with ecstatic auras have been reported by us and others; one of them even in the setting of pre-surgical electrical brain stimulation. According to the results of nuclear brain imaging and electrical stimulation, the common seizure localization in those patients appeared to be the anterior-dorsal insular cortex, where we thus propose to locate this rare ictal phenomenon. Here we summarize the role of the multiple cognitive, affective, sensory and autonomic functions of the insular cortex, which may be integrated into the creation of self-awareness, and how this system may become dysfunctional on several levels during ecstatic auras.

Epileptologie 2014; 31: 87 – 98

Key words: Ecstatic seizure, epilepsy, well-being, bliss, self-awareness, time dilatation, insula, MRI, PET, SPECT, electrical brain stimulation

Crises extatiques – le rôle de l'insula dans la modification de la conscience de soi

Les crises extatiques constituent une entité épileptique rare mais fascinante. Pendant les premières secondes de la crise, les auras extatiques provoquent une sensation de bien-être, de bonheur et de sérénité intense, et une conscience de soi augmentée. Ces auras sont souvent associées à une impression de temps dilaté, et peuvent être décrites comme une expérience mystique par certains patients. La neuroanatomie fonctionnelle des crises extatiques est encore débattue. Au cours des dernières années, plusieurs patients avec des auras extatiques ont été rapportés par nous-mêmes et par d'autres équipes, incluant une patiente dans le cadre d'une évaluation pré-chirurgicale de l'épilepsie avec électrodes intracérébrales. La localisation commune des crises (ou «zone symptomatique») pour quelques patients semble être le cortex insulaire antérieur-dorsal selon des résultats d'imagerie nucléaire et de stimulation cérébrale, et nous postulons donc que cette région est impliquée de façon majeure pour ce phénomène ictal rare. Nous résumerons dans cet article les rôles multiples du cortex insulaire au niveau cognitif, affectif, sensoriel (stimuli externes et internes, intéroceptifs) et végétatif (autonome), avec un phénomène d'intégration qui pourrait jouer un rôle majeur dans la conscience de soi, et nous proposerons des hypothèses sur la dysfonction de ce système à différents niveaux pendant les auras extatiques.

Mots clés : crises extatiques, épilepsie, bien-être, bonheur, conscience de soi, perception du temps, insula, IRM, PET, SPECT, stimulation électrique cérébrale

Ekstatische epileptische Anfälle und die Rolle des insulären Kortex bei einem veränderten Ich-Bewusstsein

Ekstatische Anfälle sind seltene, jedoch faszinierende epileptische Phänomene. In den ersten Sekunden eines Anfalls provozieren ekstatische Auren ein Gefühl des Wohlbefindens, der intensiven Zufriedenheit, von Glück und erweitertem Selbstbewusstsein, sie können mit dem Eindruck von gestörtem Zeitempfinden verbunden sein, und einige Patienten beschrieben sie als mystische Erfahrung. Die funktionelle Neuroanatomie von ekstatischen Anfällen ist weiterhin nicht vollständig verstanden. In den letzten Jahren wurden mehrere Patienten mit ekstatischen Auren von uns und anderen dokumentiert; eine Patientin sogar unter direkter zerebraler Elektrostimulation, im Rahmen einer prächirurgischen Epilepsie-Abklärung. Aufgrund dieser Resultate und der nuklearmedizinischen Bildgebung scheint sich das Anfallskorrelat im anterior-dorsalen Kortex der Insula zu befinden, wo wir demzufolge dieses seltene iktale Phänomen lokalisieren würden. Im Folgenden fassen wir die Rolle der vielfältigen kognitiven, affektiven, sensorischen und autonomen Funktionen des insulären Kortex zusammen und diskutieren ihre Rolle im Aufbau des Ich-Bewusstseins (self-awareness) und, wie dieses System im Rahmen von ekstatischen Anfällen gestört sein kann.

Schlüsselwörter: ekstatische Anfälle, Epilepsie, Wohlbefinden, Glück, Selbstbewusstsein, Zeitwahrnehmung, Insula, MRT, PET, SPECT, kortikale Elektrostimulation

Introduction

– "He fell to thinking, among other things, about his epileptic condition, that there was a stage in it just before the fit itself (if the fit occurred while he was awake), when suddenly, amidst the sadness, the darkness of soul, the pressure, his brain would momentarily catch fire, as it were, and all his life's forces would be strained at once, in an extraordinary impulse. The sense of life, of self-awareness, increased nearly tenfold in these moments, which flashed by like lightning. His mind, his heart were lit up with an extraordinary light; all his agitation, all his doubts, all his worries were as if placated at once, resolved in a sort of sublime tranquility, filled with serene, harmonious joy, and hope, filled with reason and ultimate cause. But these moments, these glimpses were still only a presentiment of that ultimate second (never more than a second) from which the fit itself began. That second was, of course, unbearable. Reflecting on that moment afterwards, in a healthy state, he had often said to himself that all those flashes and glimpses of a higher self-sense and self-awareness, and therefore of the "highest being", were nothing but an illness, a violation of the normal state and if so, then this was not the highest being at all but, on the contrary, should be counted as the very lowest. And yet he finally arrived at an extremely paradoxical conclusion: "So what if it is an illness?" he finally decided. "Who cares that it's an abnormal strain, if the result itself, if the moment of the sensation, remembered and examined in a healthy state, turns out to be the highest degree of harmony, beauty, gives a hitherto unheard-of and unknown feeling of fullness, measure, reconciliation, and ecstatic, prayerful merging with the highest synthesis of life?"[1] p. 225f

In these words Prince Myshkin reflects the moments of his epileptic condition in Dostoevsky's "The Idiot". For a long time those sentences were regarded as a product of the novelist's artistic talent. Since recently only, we might suppose that they, in fact, realistically describe the great novelist's own personal experience with ecstatic auras [1, 2], and Dostoevsky's testimony can be considered the first appearance of ecstatic auras in literature [3]. However, the existence of ecstatic seizures was initially even denied by some leading epileptologists [4, 5], for review see also [6, 7] and its further documentation was only scarce, probably also because the "hallucination of emotion" [8] seems abnormal to such an extent that patients often are reluctant to divulge such personal feelings; the experience seems "beyond what can be described in words" [9]. The frequency of such cases is therefore probably underestimated [6, 7, 9 - 18]. In order to find those rare cases, the epileptologist needs to address the possibility of ecstatic auras directly with the patient. And in turn, he also needs to recognize typical ecstatic elements in a patient's report. Patient descriptions of ictal episodes with emotional disturbances strongly depend on vocabulary, intelligence, and power of introspection [8]. Some patients have troubles finding appropriate words, or give very simplified descriptions (e.g. feeling of warmth rising in the body, "rising in the head, like bubbles in the head", see below). The fearful apprehension of the imminent complex focal or secondary generalized tonic-clonic seizure can also obscure the ecstatic aura.

Semiology of ecstatic seizures and patients' testimony

While a total of about 30 patients describing ecstatic auras are reported in literature [8 - 10, 12 - 18], we had the chance to meet and document eight additional patients during the last six years [3, 19 - 21]. These patients were between 17 and 64 years old, and engaged in all kinds of professions, e.g. female teacher, male electronics assembler, male office worker, female architect, male apprentice farmer, male philosopher etc., and from different nations as Switzerland, France, Spain, United States. Their descriptions of their own ictal events, although varying in detail and complexity, condensate a semiology of ecstatic auras comprising several typical features [3, 20].

Below we report some of the key sentences of their testimony according to different semiological elements, which are feelings of heightened well-being, enhanced self-awareness, dilated time perception, bliss/intense serenity [3, 19, 20]. Sometimes feelings of overload, of mystic experience or even of intricate anxiety are described.

Heightened well-being. One of the first mentioned features, in all patients, was the "very pleasant filling of the whole body with a wave of warmth or well-being."

– "It was something that I have never felt before. It felt as though my body was filling up with a sensation which was quite surreal. The feeling was almost out of this world." – "[...] a halo, something pleasant which fills my inner body, wrapping me, with a rapid crescendo. It is a well-being inside, a sensation of velvet, as if I were sheltered from anything negative. I feel light inside, but far from being empty. I feel really present. Something has taken possession of my body, to feel really good..." – "rising in the head, like bubbles in the head." – "the sensation was a feeling of pleasure. I felt intensely well in my body." – "My inner body rises from an unalterable bliss [...] it is an unconditional, privileged moment of inhaled sensations. My body and my head may interact differently to what every human knows. It is a sensation that is not common, something to discover."

Enhanced self-awareness. All patients reported an "augmentation" of consciousness to a vividness of perception and a clearness that was not known before.

– "During the seizure it is as if I were very, very conscious, more aware, and the sensations, everything,

seems bigger, overwhelming me." – "every sensation is stronger; for instance I see more colors than before, and I have more detailed perceptions, particularly when listening to music." – "I feel rooted to the spot with a more developed consciousness. I feel a stronger consciousness of the body and the mind, but I do not forget what is around me". – "My head fills with feelings and emotion ... I feel more conscious of myself, more concentrated on myself ... I feel more present from a psychological point of view, with more sensations. It is something very intimate. It is as if I rose a little into the air." – "It affects both the cerebral thought, which is very intense and concentrated on itself, and the physique." – "Being very conscious of myself, I feel discharged from anything else, although I do not lose consciousness." – "I feel very, very, very present at that time; the consciousness of myself is very increased, rather on a psychic point of view. I am one hundred percent concentrated on myself." – "When these boundaries are erased, a second phenomenon begins – all the ordinary facts about the environment seem suddenly to become infused with certainty and a sense of inevitability [...] One often has (what is sometimes called) an "aha!" moment when we can suddenly explain several puzzling facts simultaneously with the same answer. The sense that I had when I was experiencing some of these seizures was not unlike a continuous series of profound "aha!" moments.

Feeling of dilated time. This high clearness of consciousness can also affect time perception. Time seems to hold on at the moment.

– "I escape into the time space of my body. It is a moment of fullness in the loophole of time, a return to myself." – "Entirely wrapped up in the bliss, I am in a radiant sphere without any notion of time or space. My relatives tell me that it lasts two to three minutes, but for me these moments are without beginning and without end."

Intense serenity and bliss. There is a feeling of great serenity and peace.

– "This led to a feeling of complete serenity, total peace, no worries; it felt beautiful, everything was great." – "The immense joy that fills me is above physical sensations." – "It is a feeling of total presence, an absolute integration of myself, a feeling of unbelievable harmony of my whole body and myself with life, with the world, with the 'All'."

Feeling of overload. Some patients reported that this feeling was evolving to a very strong intensity, causing a feeling of overload.

– "It is a physical state, an overload. The feeling is intense, with a sensation of fullness." – "The sensation is certainly more intense than could be achieved with any drug." – "The pleasure goes crescendo until it reaches a peak." – "This feeling became stronger and stronger, until it became so strong that it was unbearable and led to a loss of consciousness."

Mystic/religious experience. Some patients reported strong religious or religious-like feelings:

– "Maybe the closest sensation that I know would be an orgasm, but what I felt was not at all sexual. I have no religious feeling, but it was almost religious." – "a wellbeing of almost spiritual consonance" – "These experiences brought me confidence. They confirm that there is something that surpasses us." – "It is a big happening in your life to have these seizures. Thanks to these experiences, I do not fear death anymore. I see the world differently."

Anxiety. In some cases the experience of a generalized seizure after the ecstatic aura or of a loss of consciousness (secondary "complex" focal seizure) led to increased anxiety in expectation of a new seizure.

– "... soon after the very first seizures, an anxiety intermingled very rapidly with the bliss sensation" – "...because of the anticipated fear of how he would appear to other people during his complex focal seizures. However, as the bliss increased, it overcame the associated anxiety." – "His first seizure was the most pleasant because the following ones included a feeling of fear and anxiety as he knew they would end in a generalized tonic-clonic seizure."

Seizure trigger. Some patients described that their ecstatic seizure could be triggered by a positive emotion:

– "A joy or a sense of relief can trigger seizures." – "a tractor with the harvest, nice photos, a nice color, a flower, a nice landscape, a bird singing, grazing animals, branches that move with the wind, a beautiful woman." – "or on the occasion of a kiss, a caress, a nice thought about someone, a hope."

Etiological considerations

There is no doubt that ecstatic auras emerge of focal epilepsy. In the first reports of patients with ecstatic seizures, usually a temporal lobe origin was suspected [6, 7, 9-18], yet without demonstration of any precise localization [3]. Indeed, some cases of ecstatic seizures displayed findings suggestive of anterior temporal lobe involvement, e.g. an anterior-temporal tumor [13], or left anterior temporal interictal discharges in the EEG [15, 18]. However, there were some inconsistencies in the reported cases as to the semiologic-anatomical correlation, e.g. in one case showing calcifications of the hippocampus, the ecstatic seizures occurred much later than the other ictal symptoms [11], or in another case, the ecstatic seizures disappeared after the neurosurgical treatment of an occipital arterio-venous malformation, although the gliotic ipsilateral hippocampus was not removed [13]. In another case, the ecstatic symptoms appeared not before but after removal of the sclerotic part of the mesiotemporal lobe [15]. Finally, already during Dostoevsky's auras laryngeal spasms were reported [22], a symptom that is quite specific for insular seizures [23].

Half of the eight patients we met suffered from epileptogenic brain lesions like meningiomas (n=2), xanthoastrocytoma (n=1) and a dysembryoplastic neuroepithelial tumour (DNET; n=1), with an age of onset of their epilepsy between 15 and 43 years. The four other patients had normal MRI and an age of onset of their epilepsy between 12 and 18 years. The tumoral lesions (all of low grade or benign tumoral nature) were located in the temporal pole (n=3), and in the parahippocampal region (n=1) (**Figure 1A, B, C**). Accordingly, the FDG-(fluorodeoxyglucose)-PET showed right temporal and insular hypometabolism in the patient with the DNET, right temporal hypometabolism in the patient with the parahippocampal xanthoastrocytoma, and in a third patient with normal MRI but clear temporal lobe seizure semiology, there was a hypometabolism in the anterior part of the right temporal lobe [19]. Two of the patients with a temporal pole lesion showed also an anterior insular involvement on the ictal SPECT (tracer injected during the ectstatic aura; **Figure 1D, E**) [3, 20]. To note, other authors also reported a hyperactivation of the left anterior insula during the ictal SPECT in another patient [24].

Based on the analysis of these patients with ecstatic auras, we have recently proposed that ecstatic symptoms originate in the anterior insula [3], even when the epilepsy is related to a temporopolar lesion. This interpretation appears consistent with a large body of recent findings on the functions of this brain region [25, 26],

Since the late 1940s, the possibility of seizures originating from the insular cortex has come into view of epileptologists [27, 28], however for a very long time it was nearly impossible to disentangle insular seizures from MTL seizures due to the very similarity of the symptoms, because seizures of MTL origin seem to often also invade the insular cortex [29]. It was only with the recent advent of sophisticated stereo-guided insertion of depth electrodes, allowing to place them precisely deep in the insular cortex, together with video-EEG evaluation, that specific features of insular seizures could systematically be investigated. The typical insular onset occurred in full consciousness, beginning with laryngeal constriction, dyspnea, unpleasant perioral or somatic paresthesias, and dysarthric speech, followed by a complex partial seizure [23]. Therefore if on video-EEG recordings this clinical sequence is observed at the onset of a complex partial seizure in TLE patients, it strongly suggests actual seizure-onset in the insular cortex, not in the mesiotemporal region [23]. In their study of electrical stimulation on the implanted insular electrodes of 50 TLE patients, Isnard et al. [23] reported only 5 patients having seizures originating within the insula, one of whom reported symptoms of mirth and clairvoyance, suggesting a hypothetical possibility of ecstatic auras.

Ecstatic seizures caused by electrical stimulation

The proof of concept for the anterior-dorsal insular localization of ecstatic seizures was given when we met another patient, a 23 year-old right-handed woman, in pre-surgical evaluation for her refractory right temporal lobe seizures. Since the age of 12 she had reported intense feeling of bliss and well-being, consisting of "sensations of airflow" from her stomach, associated with a feeling of "floating". In the moments before seizure she reported enhanced sensory perception, especially of intense colors, and a feeling of dilated time. Her seizures evolved then into loss of consciousness together with gestural and oro-alimentary automatisms [19].

After her brain MRI was unremarkable, she was implanted with intracerebral electrodes covering the right temporal lobe and the insular cortex (**Figure 2**) for presurgical evaluation (phase II). Her seizures were recorded, and were found to originate always from the right mesiotemporal region, rapidly propagating (<1sec) to the anterior-dorsal insula. During systematic testing of implanted electrodes with electrical stimulation (50Hz, 0.5 – 2 mA, 1ms pulse width; the patient was blinded), none of the stimulated electrodes triggered a seizure. Stimulation of the right amygdala elicited strong unpleasant sensations like anxiety and epigastric pressure, however the stimulation of the anterior-dorsal insular electrode (OF1 – 2) suddenly provoked a "very pleasant funny sensation of floating and a sweet shiver" in her arms, identical to her usual ecstatic auras. Stimulations between 1mA and 1.6mA provoked this sensation, but not below 1mA. None of the stimulation on other electrodes had a similar effect [19].

To date this is the only published case describing induction of ecstatic symptoms by intracerebral electrical stimulation. While induction of unpleasant emotions have been reported during stimulation of amygdala and hippocampus already long ago [30, 31], moderately pleasant feelings have been induced in left amygdala in a more recent study [32]. Electrical stimulations of the insula have elicited a variety of symptoms in different systems, depending on the stimulated insular subregion, such as interoception, somatosensation, emotion, cognition, gustation, olfaction (also pleasant) [28, 33], but no ecstasy-like feelings, except possibly in one study, where a "weird feeling of flying away" was reported in one patient [34]. As reported above, one study recorded a spontaneous seizure starting with a feeling of clairvoyance and mirth, which was correlated with epileptic discharges in the insula, which did not spread to other cortical regions in the intracranial EEG recording [23].

The case of our patient demonstrates several highly

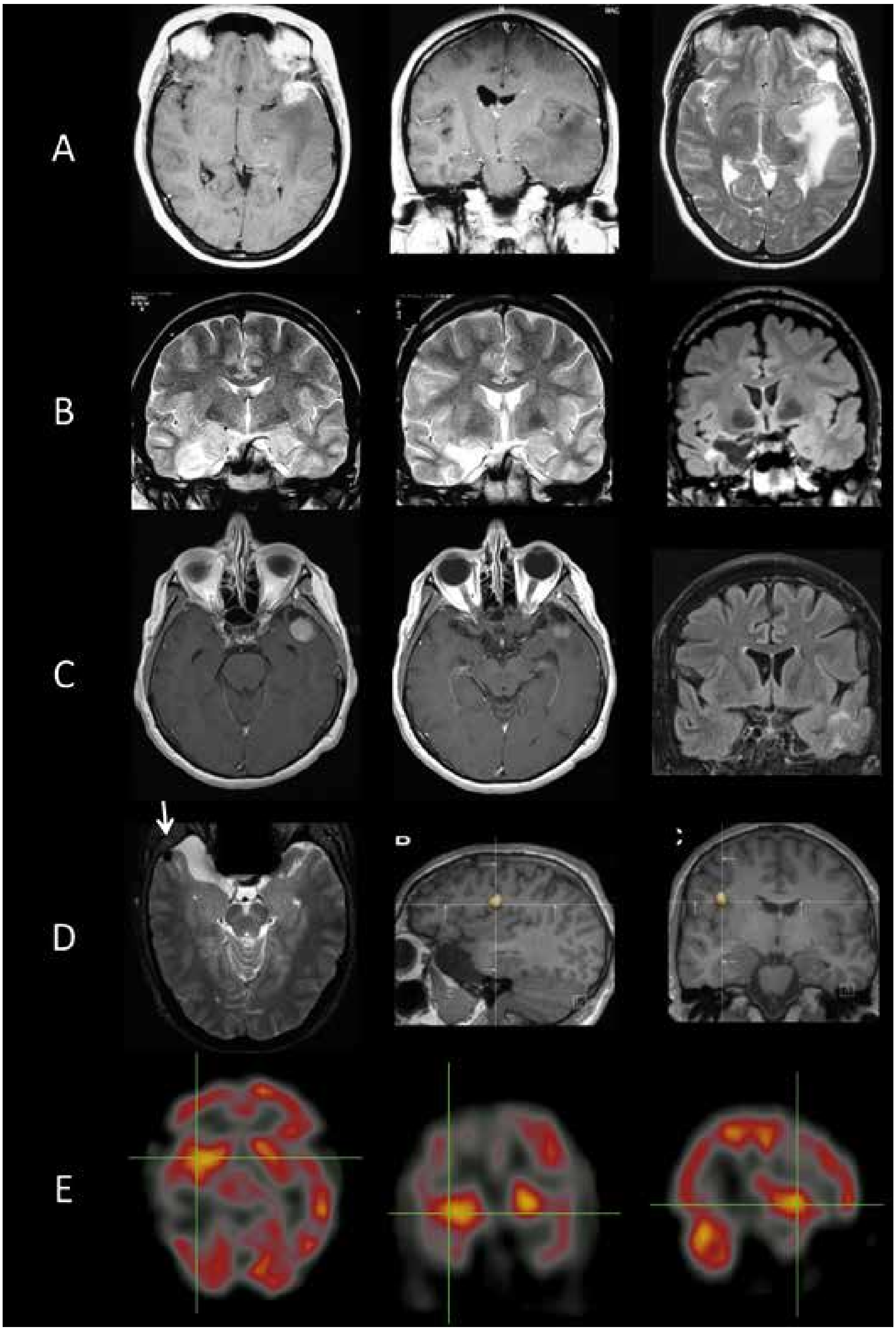

Figure 1: Brain imaging of patients with brain lesions causing ecstatic auras[1].

A. MRI of a 53-year-old woman showing a left sphenoidal meningioma causing extensive edema involving the whole temporal lobe and extending up to the anterior insula (from left to right: post-contrast T1-weighted axial and coronal image, T2-weighted axial image).

B. MRI of a 37-year old man with a xanthoastrocytoma. Left: Presurgical T2-weighted coronal image (1996) showing a right temporal lobe tumor in the parahippocampal gyrus. The border of the tumor is close to the inferior part of the anterior insula. Middle: Post-operative T2-weighted coronal images (1997), showing that the gliosis reaches the anterior insula. Right: FLAIR coronal image, 12 years after the resection (2008).

C. MRI of a 64-year-old woman showing the recurrence of a meningioma in the left temporal pole. Left and middle: Postcontrast T1-weighted axial images, FLAIR coronal image showing that the edema and/or gliosis reaches the temporal operculum, impinging on the anterior insula.

D. MRI and ictal SPECT images superimposed (SISCOM[2]) of a 17-year-old man. Left: The gradient echo T2* axial image shows a small round (hypointense) tumor in the right temporal pole and a neighboring arachnoid cyst. Middle and right image: sagittal and coronal view, showing a maximally increased blood flow at the junction of the right dorsal mid-insula and the central operculum.

E) Ictal SPECT images of a 37-year-old patient (the same as in B.) using technetium-99m-ethylcysteinatedimer (99mTc-ECD), in axial, coronal and sagittal view, showing increased blood flow maximal in the right anterior insula. The ictal SPECT was performed postsurgically (2005) during a seizure with an ecstatic aura. The analysis program BRASS (Brain Registration and Analysis Software Suite) was used for automatic fitting of brain perfusion scans and quantification and localization of abnormal perfusion regions.

1) Images used from [3, 20]

2) SISCOM = Subtracted ictal SPECT coregistered with MRI [99]: Ictal/interictal technetium-99m HMPAO (99mTc-HMPAO) SPECT subtraction using BRASS analysis program. The software allows automatic fitting of brain perfusion scans and subtraction.

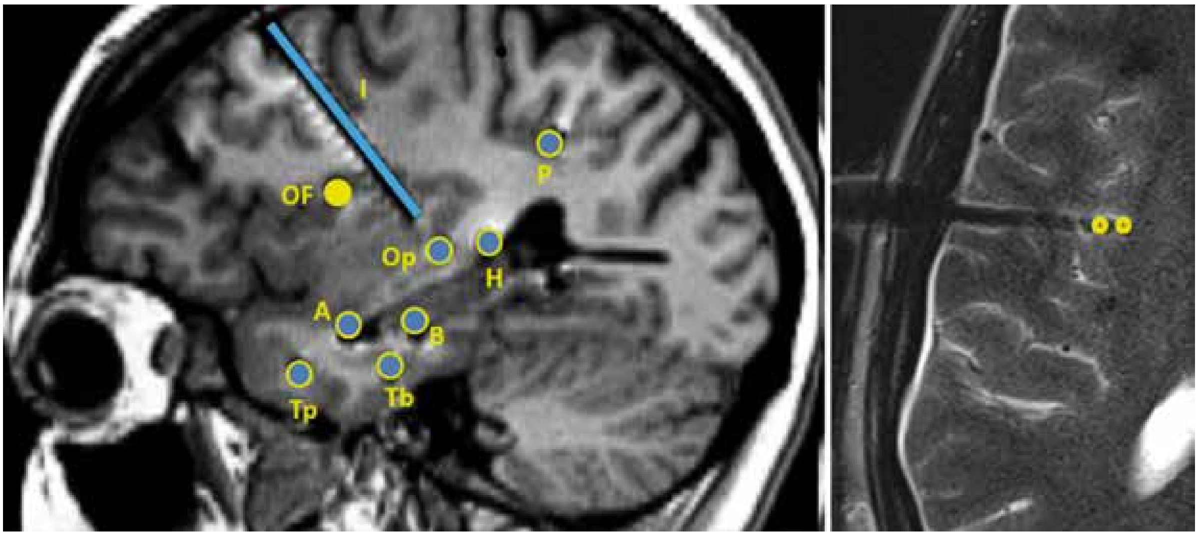

Figure 2: Sagittal view of the patient's MRI with localization of intracerebral electrodes. Nine electrodes were implanted with each of them containing 10-15 contacts. Electrodes A, B and Tb explore the right medial temporal lobe. Electrodes I (insula) and OF (frontal operculum) reach the right insular cortex. Right part: axial view, with detail of the electrode OF reaching the anterior-dorsal part of the insula. The two first contacts (1 and 2) are highlighted in yellow. Bliss sensation was elicited by bipolar stimulation (1-1.6 mA, 4 sec-train duration) of these contacts.

Tp, temporal pole; Tb, temporobasal cortex (lateral contacts) and entorhinal cortex (medial contacts); A, middle temporal gyrus (lateral contacts) and amygdala (medial contacts); B, middle temporal gyrus (lateral contacts) and anterior hippocampus (medial contacts); H, superior temporal gyrus; P, inferior parietal lobule (lateral contacts) and posterior cingulate cortex (medial contacts); OF, frontal operculum and anterior insula (medial contacts); I, middle insula; Op, parietal operculum. Reprinted from [19].

interesting facts which complete our understanding of the function of the insula and of brain mechanisms leading to ecstatic seizures: First, the intense feelings of bliss with interoceptive and emotional components can be induced by the stimulation of a relatively small area within the right anterior-dorsal insula. Second, the stimulation was low in intensity, and there was no after-discharge effect, which further confirms the very localized region for this blissful feeling. Moreover and very importantly, this region did not correspond to the initial seizure generator zone, but was the symptomatic zone of seizure propagation, meaning that functional or plastic tissue alteration is not necessarily to be expected in this region. And finally, the fact that the patient reported such ecstatic symptoms since the very beginning of her epilepsy suggests that this anterior-dorsal insular region likely fulfilled a similar function originally, before any seizure related brain tissue destruction occurred in this place.

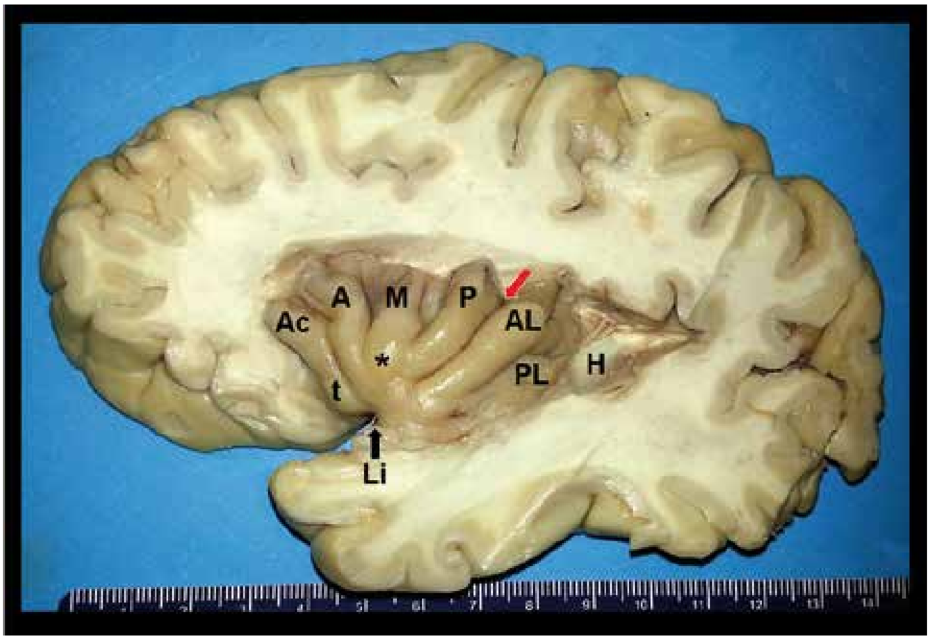

Figure 3: Anatomy of the insula and its relationship with the sulci of the inferior frontal lobe, as disclosed in the depth of the lateral fissure. The central sulcus (red arrow) divides the lateral surface of the insula into a large anterior insular lobule composed of the anterior short (A), middle short (M) and posterior short (P) insular gyri that converge to the apex of the insula (*) and a small posterior insular lobule is composed of the anterior long (AL) and posterior long (PL) insular gyri that converge to the limen insulae (Li, black arrow). The anterior face of the insula displays a constant transverse insular gyrus (t) that connects with the orbital surface of the frontal lobe and a variably present accessory insular gyrus (Ac) further superiorly. H = the posterior medial stub of the transverse temporal gyrus of Heschl (primary auditory cortex) that was resected to uncover the posterior long insular gyrus. Figure courtesy of Drs. Thomas P. Naidich and Mary E. Fowkes, the Icahn School of Medicine at Mt. Sinai, New York.

Neuroanatomy of the insula and its functions

The insula lies hidden deep under the temporal lobe, the frontal and parietal opercula, within the Sylvian fissure, as well as under arterial and venous vessels, making its access particularly difficult. It spans Brodmann Areas BA13 to BA16 [35], and it is cytoarchitectonically subdivided in a rostroventral agranular zone and a dorsocaudal granular zone [36 - 38] (**Figure 3**). The rostroventral agranular zone and its immediate surroundings are connected with the limbic structures such as amygdala and posterior orbitofrontal and anterior cingulate cortices [39]. The borders and connections of the dorsocaudal granular zone are much less clear and still under debate [38], as it is largely connected to many other brain regions as, e.g. parietal and mesio-prefrontal cortex as well as anterior cingulate and temporal cortex [38, 40, 41]. Inbetween the agranular and the granular zones, a dysgranular part has been described, which covers the anterior-dorsal and central insula [35, 42]. The insula is a relatively old structure [42], and especially the anterior part has passed through an impressive differentiation during hominoid evolution, but there is still ongoing debate about the existence of a homologue structure in primates and other animals [38, 41].

Coinciding with its wide connections, the insula is implicated in a large variety of brain functions. Auditory function, vestibular function, somatosensation, pain and temperature perception, viscerosensation, gustation, olfaction, visceromotor control, somatomotor control, motor plasticity, speech production, language, attention, cognitive control, bodily awareness, self-recognition, individual emotions, empathy [25, 38, 43], which can be grouped into four functional domains, defined as an olfacto-gustatory, a sensorimotor, a cognitive, a social-emotional domain [43]. Another meta-analysis also supports a tripartite subdivision of the insula with dorso-anterior, ventro-anterior and posterior regions, corresponding to cognitive, affective/chemosensory and sensorimotor processing, respectively [44]. The analysis over all categories except somatosensation and motion revealed an overlap on the anterior-dorsal insula, located at the dorsal end of the sulcus between the middle and anterior short gyrus [43], exactly the region where the electrodes of our patient had been placed [19].

According to the authors, the overlap in the mapping of the categories in the anterior-dorsal insula, could be due to a basic functional role that all categories have in common, which might be a general role in task processing, like starting, updating, and maintaining of a task. Given the dense interconnection between the different subparts of the insula, information flows rapidly to the anterior-dorsal insula [35, 38], and this region was recently proposed to represent the final stage of the hierarchical processing from the other subparts of the insula, i.e. starting with pure sensory information in the posterior insula, integrating emotional and cognitive valuation, and ending in the anterior-dorsal insular region with a full representation of a "sentient self", the sine qua non of self-awareness [25, 26, 43].

It is from here that goal-directed acting will occur, and one of the most influential concepts in nowadays neurobiological comprehension of decision making and choice behavior is the feedback loop of error prediction [45]: In a perpetual process the present state is extrapolated, and a prediction is generated which is then compared to the actual state. Based on the comparison the neuronal system aims to minimize the resulting error. In this evaluation loop the anterior-dorsal insula, as the center of interoception (self-sensation) and self-awareness, has been suggested to play the role of the comparator of the predicted to the present outcome [46 - 48], and the role in task-control initiation, maintenance and adjustment, in the context of switching between different mind states [49 - 51]. This model also applies to estimation and processing of risk [52, 53]. During risky decisions in gambling tasks, the anterior insula encodes the risk prediction while waiting for the outcome. Once the outcome is known, it reflects the prediction error, by acting as a comparator between predicted risk and realized risk [46, 54]. Various imaging studies have shown that the anterior insula is an important controller of switching between different tasks and states [44, 50, 55], and it is specifically sensitive to salient environmental events, with one of its core functions being to mark such events in space and time for additional processing [56 - 59]. The temporal judgement of the "nowness" has been shown to be tightly linked to the function of interoception and to emotional processing [25, 60, 61]. It is modulated by arousal, attention and the sentient processing [62]. Several imaging studies have confirmed insular implication in time judgments [63 - 68]. Craig proposed that there is a dorsal to anterior insular integration of interoceptive, sensorial and emotional information at each moment to a "global emotional moment" [25, 60], the succession of which would produce a cinematoscopic "image" of the sentient self serving as a basis for time perception with an approximate frame rate of 7 - 8 Hz (i.e. each "global emotional moment" lasting 125 - 150 ms) [3, 64].

Hypothesis of mechanisms on consciousness

Ecstatic seizures are of focal nature. The ictal discharge implicates at a certain moment the anterior-dorsal insula, the region located at the highest level of insular information processing, which has been suggested to be the neuronal correlate of self-awareness, where the "sentient self" is formed [3, 25, 60]. The already mentioned dense fiber connection of the insula with the cingulate, parietal, temporal and frontal cortex [39, 40, 42], as well as interconnection within the subparts of the insula [35 - 37, 41, 43], enable rapid seizure propagation from adjacent areas like the mesiotemporal region. This propagation likely causes the individual manifestation of ecstatic seizures with very different attendant symptoms like auditory, gustatory of olfactory sensations (depending on the exact focus of the ictal discharge) [3, 20]. Especially the mesiotemporo-insular connections serve as a direct seizure propagator to the insular region [23, 29], explaining the strongly "insular" semiology of many mesiotemporal lobe seizures. However seizures originating in the lateral temporal neocortex can propagate to the anterior insula without going through the mesiotemporal region [29]. Moreover, recordings of synchronous spikes at the temporal pole and in the insula shows an instantaneous spreading of ictal activity also from the temporal pole toward the insula [29].

On the other hand, a pure neocortical temporal symptomatology seems unlikely in patients with ecstatic auras, because the classic clinical features of lateral temporal seizures as auditory and visual illusions and hallucinations, vertiginous auras and early contralateral dystonic posturing [69], were absent in our patients. For temporal pole seizures, no specific symptoms have been described except for an earlier occurrence of loss of consciousness compared to mesiotemporal seizures [70]. Orbitofrontal propagation finally also seems unlikely to explain ecstatic semiology. Such seizures are described as sometimes complex automatisms (bizarre gesticulations and often violent movements mimicking fearful behavior with autonomic signs), as well as a sudden loss of contact [71].

There are two other areas of current research, in which very similar subjective experiences to those during ecstatic seizures are described: brain mechanisms implicated in meditation and those implicated in illicit drug addiction. We will shortly discuss them here, in order to better understand the semiologic-neurobiologic relationship of ecstatic seizures.

Brain mechanisms in addiction. Reports of experiences with use of stimulant drugs such as heroine, cocaine, amphetamine or ecstasy (3,4-methylene-dioxy-methamphetamine) usually mention strong feelings of bliss, enhanced instrospective awareness, inner peace, and the breakdown of the barrier between the subject and the surroundings, creating a heightened union with the world. Numerous recent neuroimaging studies have shown implication of the anterior insula in drug addiction [72 - 74], and the key role of this structure in the neurobiology of addictive behavior is now well established. The insula acts as integrator of interoceptive (i.e. bodily) states and conscious emotions into decision-making processes involving uncertain risk and reward [75]. For example, a positive correlation between the dose of administered cocaine and the insular activity (as well as the cingulate cortex and nucleus accumbens activity) was found in rats [76]. In nonhuman primates, cocaine administration was shown to induce immediate early gene expression in the insular and ventromedial prefrontal cortex [77]. In humans, a longer duration of cocaine dependence was shown to correlate with a reduction of gray matter volume in the insular, cingulate, and orbitofrontal cortices [78, 79]. The comparison of patients with left insular lesions and normal controls showed that the emotional effects of nicotine (a stimulant at small doses), were lost in patients with lesion and that they failed to find more pleasure in puffs with nicotine compared to puffs without nicotine [74]. The consumption of Ayahuasca tea, a central element of Amazonian shamanism which produces enhanced introspective attention and euphoria, was shown to activate bilateral anterior insula [80].

It is thus likely that the implication of the anterior insula in both illicit drug use and ecstatic seizures explain the similarity of subjective symptoms [3].

Brain mechanisms implicated in meditation. With some variation, depending on the type of meditation practiced, one of the general aims of meditation techniques is to bring the conscious mind into a state of enhanced awareness of the present moment, and to minimize mind wandering. With these techniques often a cognitive reappraisal of emotionally salient sensory events is attempted, a process for which again the anterior insula has been shown to be involved [81 - 84]. For example, functional brain imaging studies have reported that modulation of state anxiety by mindfulness meditation engaged a network of brain regions including the anterior insula [81]. Activation in the dorso-anterior insula during meditation correlated with the self-reported intensity of meditation [83], and was higher in advanced meditators (>10’000 hours of practice) compared to beginners [55]. Conversely, structural imaging studies have demonstrated a thicker cortex [85], with more gray matter concentration [86], and a stronger gyrification in the anterior insula in meditators compared to controls, which in turn also correlated with the number of meditation years [82] and with increased pain tolerance [87].

Taken together, the insula’s multiple functions, especially those of the anterior-dorsal subpart interestingly could integrate the symptoms of ecstatic seizures. When we go back to the semiologic elements taken from the patients’ descriptions, we can try to hypothesize what might explain them in the light of our neurobiologic knowledge about the insula.

Enhanced self-awareness and heightened well-being. The anterior insula is the anatomical substrate for the capacity of self-awareness, represented in the “global emotional moments”, integrated from multisensory input and the processing of interoception [25]. An ictal storm in this region will alter this integrative cycle and mostly provoke unpleasant feelings [23] but it is also possible that it elicits very pleasant ones [8, 16]. The ictal activation of the saliency detection system will then add a feeling of importance, of heightened consciousness of any stimulus [3, 20, 21, 25]. The anterior-dorsal insula essentially participates in the self-reflective network, maintaining a coherent first-person perspective, on the bases of its connections towards inferior parietal lobe (temporo-parietal junction) [25, 35, 40, 50, 88, 89].

Feeling of dilated time. As above-mentioned, time perception has been related to self-referential processing [63], given the insular integration of interoceptive, sensorial and emotional information to a “global emotional moment” [3, 25, 60] in a perpetual cycle. The sampling rate of this integration is not fixed, but is modulated by the salience of the input, i.e. salient moments increase the sampling rate, leading thus to a subjective dilation of time. In an ecstatic aura, when each moment is perceived as salient, we propose that the extremely high number of consecutive salient moments would increase the sampling rate to a maximum, leaving the patient subjectively timeless in a sustained state of “present-moment awareness” [21]. Other insular functions like the task monitoring and task switching, or the prediction error [20] equally display cyclic properties and might equally contribute to the altered feeling of time.

Intense serenity versus anxiety. The human brain is a prolific generator of beliefs, and personhood is the result of the capacity to evaluate new propositional truth in the light of all the others that are already accepted [90]. Decision-making in uncertainty has been shown to be altered in patients with anxiety disorders, where there is a particular intolerance of uncertainty and ambiguous situations [91, 92]. These patients, when confronted with a mismatch between predicted state and actual state, interpreted neutral stimuli even as threatening, evoking anxiety and avoidance behavior, which correlated with enhanced anterior insula activity [92]. Also in obsessive-compulsive disorder, specifically characterized by a high subjective experience of doubt, patients had a greater activation in anterior insula and frontal operculum in an error-eliciting interference task [93], and were shown to have a larger gray matter volume in the anterior insular cortex [94, 95]. During ecstatic seizures these mechanisms of comparison between predicted states and actual states seem to be blocked leading to the intense serenity and absence of any anxiety. The sustained state of conscious awareness of the present moment, which takes away the worries about the past and the future, seems to express itself in a feeling of inner peace [19 - 21].

Religious interpretation by some patients. When the comparator between the predicted and the actual state no longer functions during ecstatic seizures, there is no mismatch. This could lead to a feeling of clarity and certainty, because the predicted states are preserved. A long-lasting state without any mismatch during several seconds is like a strong contemplation and can be blissfull and serene, as experiences in meditation [96], or as "state of union with God" [97].

Outlook and open questions

While we can now explain a great deal of the initially mysterious Dostoevsky's syndrome, and while the neurobiological background starts to be clarified, we still face many unanswered questions. Is the presentation of ecstatic seizures sufficiently explained with insular discharges or is there necessity of additional involvement of any other structures, or of so far unknown conditions? Why did the systematic electrical insular stimulation of so many other patients across several studies never provoke ecstatic seizures? Could it be explained by the researchers' focus of interest? What role does lateralization play and is there a preferential side? Lastly, the Geschwind's syndrome [98], an interictal syndrome reported in some patients with temporal lobe epilepsy consisting of the association of hyperreligiosity, hypergraphia and hyposexuality, could have some overlapping features with ecstatic seizures, yet among our patients we have not found a patient with Geschwind's syndrome.

Most probably many of those questions could be answered with the observation of a higher number of cases, and we are still looking for further patients presenting ecstatic ictal experience. Therefore, if you, after having read this article, encounter such patients, please feel free to get in contact!

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